Lungscape: resected non-small-cell lung cancer outcome by clinical and pathological parameters

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Abstract: INTRODUCTION The Lungscape project was designed to address the impact of clinical, pathological, and molecular characteristics on outcome in resected non-small- cell lung cancer (NSCLC). MATERIALS AND METHODS A decentralized biobank with fully annotated tissue samples was established. Selection criteria for participating centers included sufficient number of cases, tissue microarray building capability, and documented ethical approval. Patient selection was based on availability of comprehensive clinical data, radical resection between 2003 and 2009 with adequate follow-up, and adequate quantity and quality of formalin-fixed tissue. RESULTS Fifteen centers contributed 2449 cases. The 5-year overall survival (OS) was 69.6% and 63.6% for stages IA and IB, 51.6% and 47.7% for stages IIA and IIB, and 29.0% and 13.0% for stages IIIA and IIIB, respectively ($p < 0.001$). Median and 5-year relapse-free survival (RFS) were 52.8 months and 47.3%, respectively. Distant relapse was recorded for 44.4%, local for 26.0%, and both for 16.9% of patients. Based on multivariate analysis for the OS, RFS, and time to relapse, the factors significantly associated with all of them are performance status and pathological stage. CONCLUSION The aim of this report is to present the results from Lungscape, the first large series reporting on NSCLC surgical outcome measured not only by OS but also by RFS and time to relapse and including multivariate analysis by significant clinical and pathological prognostic parameters. As tissue from all patients is preserved locally and is available for detailed molecular investigations, Lungscape provides an excellent basis to evaluate the influence of molecular parameters on the disease outcome after radical resection, besides providing an overview of the molecular landscape of stage I to III NSCLC.

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Lungscape: Resected Non–Small-Cell Lung Cancer Outcome by Clinical and Pathological Parameters

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Introduction: The Lungscape project was designed to address the impact of clinical, pathological, and molecular characteristics on outcome in resected non–small- cell lung cancer (NSCLC).

Materials and Methods: A decentralized biobank with fully annotated tissue samples was established. Selection criteria for participating centers included sufficient number of cases, tissue microarray building capability, and documented ethical approval. Patient selection was based on availability of comprehensive clinical data, radical resection between 2003 and 2009 with adequate follow-up, and adequate quantity and quality of formalin-fixed tissue.

Results: Fifteen centers contributed 2449 cases. The 5-year overall survival (OS) was 69.6% and 63.6% for stages IA and IB, 51.6% and 47.7% for stages IIA and IIB, and 29.0% and 13.0% for stages IIIA and IIIB, respectively ($p < 0.001$). Median and 5-year relapse-free survival (RFS) were 52.8 months and 47.3%, respectively. Distant relapse was recorded for 44.4%, local for 26.0%, and both for 16.9% of patients. Based on multivariate analysis for the OS, RFS, and time to relapse, the factors significantly associated with all of them are performance status and pathological stage.

Conclusion: The aim of this report is to present the results from Lungscape, the first large series reporting on NSCLC surgical outcome measured not only by OS but also by RFS and time to relapse and including multivariate analysis by significant clinical and pathological prognostic parameters. As tissue from all patients is preserved locally and is available for detailed molecular investigations, Lungscape provides an excellent basis to evaluate the influence of molecular parameters on the disease outcome after radical resection, besides providing an overview of the molecular landscape of stage I to III NSCLC.

Key Words: NSCLC, TNM stage, Surgery, Patients' and pathological characteristics, Outcome.

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¶¶¶For details on ETOP Lungscape Investigators, see Appendix.

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The seventh edition of the tumor, node, metastasis (TNM) system reliably serves in estimating the prognosis of patients with non–small-cell lung cancer (NSCLC) and provides the basis for decisions on treatment strategies. For operable patients with earlier stages of disease, surgery remains the established standard of care. For patients with a complete resection of pathological stage II and III tumors, adjuvant chemotherapy has been proven to increase the 5-year survival by an absolute 4.0%,[1] whereas a benefit from adjuvant radiotherapy remains uncertain and, if existing, probably is restricted to stage III disease.

The seventh edition of the TNM classification of NSCLC was published in 2009. It is built on the retrospective analysis of patients from 46 sources from more than 20 countries treated by all modalities from 1990 to 2000 to guarantee a 5-year follow-up. The survival analysis was based on 67,725 cases of NSCLC, of which data on pathological stage were available in 16,952 cases.[2]

Since the identification of activating mutations in the epidermal growth factor receptor gene as a molecular driver for a subset of NSCLC, it has become recognized that adenocarcinoma of the lung no longer represents a single entity but rather comprises a growing spectrum of distinct molecular subtypes for which specific systemic therapies have entered clinical practice or are currently under investigation.[3] A similar, potentially even more complex picture is emerging in squamous cell lung cancer.[4]

The Lungscape project was designed to address the challenges of studying the molecular epidemiology of lung cancer and to expedite our knowledge of current and evolving clinical and molecular biomarkers. As the basis of this work, a decentralized biobank with fully annotated tissue samples was created to elucidate the outcome of clinically, pathologically, and molecularly characterized subgroups of resected stage I to III NSCLC. Fifteen centers contributed their data on a total of 2449 patients. The aim of this study is to describe the outcome, including overall survival (OS), as reported in the *International Association for the Study of Lung Cancer* database,[2] but also for the first time in a large surgical series, relapse-free survival (RFS) and time to relapse (TTR), according to pathological stage, histology, and clinical parameters for 2449 patients with resected NSCLC.

PATIENTS AND METHODS

Patient Selection and Data Capturing

Data on patients with pathological stage I to III NSCLC in 14 European and one Chinese center have been collected retrospectively, according to the Lungscape protocol. Selection criteria for participating centers included sufficient numbers of cases, availability of a full clinicopathological data set, tissue microarray building capability, and documented ethical approval for investigations on tissue samples and sharing associated clinical data. Patient selection was based on radical surgical resection performed between January 1, 2003, and up to December 31, 2009, allowing for a follow-up of at least 3 years, comprehensiveness of clinical annotation, and adequate formalin-fixed paraffin-embedded tissue.

After data capture in the iBiobank, a central electronic database used to store anonymized comprehensive molecular and clinical data, a systematic medical data review of every case was performed to check for plausibility, to optimize staging accuracy under the seventh TNM classification,[2] and to confirm availability of tissue. To facilitate quality assurance in regard to tissue and pathological staging, upload of the original anonymized pathology reports to the iBiobank database was mandatory. Clinical data were categorized into mandatory parameters necessary for case submission and acceptance by central review, and desirable parameters as listed in Supplementary Table 1 (Supplemental Digital Content, http://links.lww.com/JTO/A687). Tissue tracking was also systematically recorded, allowing verification of biological material availability.

Statistical Analysis

Comparison of patient and tumor characteristics was performed by Fisher's exact and Mann-Whitney tests for categorical and continuous variables, respectively. Adjustment for multiple testing was not used. All tests performed were two-sided. Statistical analysis was performed in SAS version 9.3.

Log-rank tests and Cox model Wald tests were used for comparisons of time-to-event end points between subgroups of interest. The outcome is measured by three time-to-event end points: OS, RFS, and TTR. OS is defined as time from surgery until death. RFS is defined as time from surgery until documented relapse or death from any cause. To avoid competing risks of death and better define the surgical outcome, the end point of TTR is used. TTR is defined as the time from surgery until documented relapse or death due to the disease. The difference between RFS and TTR lies in the fact that all deaths—regardless of the cause of death—are counted as RFS events, whereas only deaths caused by the disease are counted as TTR events. For cases with documented relapse and missing relapse date, the date of relapse is substituted by the death date or the last follow-up date, if the patient is still alive. For all time-to-event end points, if the relevant event was not observed, the last day of follow-up is taken as the censoring date. Landmark analyses at different time points were used for exploring the association of OS with RFS and TTR.

Cox proportional hazards regression was used to model the association of the time-to-event end points with the characteristics of interest and estimate hazard ratios (HRs) along with their corresponding 95% confidence intervals. In multivariate models, using the backward selection method, with removal criterion of 10%, the association with outcome of each factor in the presence of others in the model was explored. Observed differences in time-to-event end points were depicted via Kaplan–Meier curves. Median follow-up time was estimated using the reverse censoring method for OS.

Cumulative incidence plots were created to explore time-to-local and time-to-distant recurrence.[5] Patients with missing site of relapse were excluded from this analysis, whereas patients with both types of recurrence were considered as having distant recurrence.

RESULTS

As of March 11, 2013, a total of 2449 retrospective cases of NSCLC have been captured in the Lungscape iBiobank (Supplementary Table 2, Supplemental Digital Content, http://links.lww.com/JTO/A687). For all patients, surgery was performed no later than 2009 (91.5% with surgery from 2003 to 2009), and complete information was available on medical history, histology, and pathological TNM staging. Almost all patients with status alive at last follow-up have been followed for more than 3 years, with the exception of 43 patients with follow-up between 2 and 3 years.

Patient, Tumor, and Treatment Characteristics

The majority of patients are men (65.4%), with median age at surgery of 66 years (range, 23–90 years), and of white ethnicity (93.9%). Most are characterized as either current (31.9%) or former smokers (49.8%), whereas 13.8% are recorded as never smokers. Smoking history is unknown for only 4.5% of patients. Performance status (PS) at diagnosis is captured for 52.1% of the cohort, and the overwhelming

majority of these patients have a PS of 0 (61.2%) or 1 (35.6%). Previous history of cancer was reported in 14.1% of patients, whereas the majority of patients had no cancer previously (71.1%). Information is lacking for 14.7% of the cohort (Table 1). The majority of patients have adenocarcinoma (51.2%) and 40.7% squamous cell histology. The remaining

TABLE 1. Patient, Tumor, and Treatment Characteristics (n = 2449)

Characteristics	Total (n = 2449)
Sex, *n* (%)	
Male	1602 (65.4)
Female	847 (34.6)
Age at surgery (yr)	
n (%)	2448 (99.9)
Mean (95% CI)	65.0 (64.6–65.4)
Median (min–max)	65.9 (22.6–89.5)
Ethnicity, *n* (%)	
White	2300 (93.9)
Asian (East/South)	141 (5.8)
South American	4 (0.2)
African	3 (0.1)
Missing	1 (0.0)
Smoking history, *n* (%)	
Current	782 (31.9)
Former	1219 (49.8)
Never	338 (13.8)
Unknown	110 (4.5)
Performance status at diagnosis, *n* (%)	
0	781 (31.9)
1	454 (18.5)
2	32 (1.3)
3	9 (0.4)
Unknown	551 (22.5)
Missing	622 (25·4)
Previous history of cancer, *n* (%)	
No	1742 (71.1)
Yes	346 (14.1)
Missing	361 (14.7)
BMI (kg/m^2)	
n (%)	1186 (48.4)
Mean (95% CI)	25.3 (25.1–25.6)
Median (min–max)	24.9 (14.8–59.1)
Histology, *n* (%)	
Adenocarcinoma	1255 (51.2)
Squamous cell	997 (40.7)
Large cell	107 (4.4)
Adenosquamous	54 (2.2)
Combined/mixed (with or without parts of SCLC)	28 (1.1)
Sarcomatoid	8 (0.3)
Pathological stage, *n* (%)	
IA	560 (22.9)
IB	644 (26.3)
IIA	415 (16.9)
IIB	292 (11.9)
IIIA	499 (20.4)
IIIB	39 (1.6)
Localization of primary tumor, *n* (%)	
Upper lobe R	757 (30.9)
Upper lobe L	666 (27.2)
Lower lobe L	383 (15.6)
Lower lobe R	341 (13.9)
Middle lobe R	127 (5.2)
Overlapping over several lobes	110 (4.5)
Central tumor	64 (2.6)
Missing	1 (0.0)
Tumor size (cm)	
n (%)	2447 (99.9)
Mean (95% CI)	4.0 (3.9–4.1)
Median (min–max)	3.5 (0·2–16.0)
≤4	1564 (63.9)
>4	883 (36.1)
Pleural invasion, *n* (%)	
No	1610 (65.7)
Yes	814 (33.2)
Missing	25 (1.0)
Type of surgery	
Anatomy, *n* (%)	
Lobectomy	1791 (73.1)
Pneumonectomy	333 (13.6)
Bilobectomy	157 (6.4)
Wedge resection	88 (3.6)
Segmentectomy	39 (1.6)
Other	26 (1.1)
Missing	15 (0.6)
Technique, *n* (%)	
Open thoracotomy	2246 (91.7)
Thoracoscopy	118 (4.8)
Missing	85 (3.5)
Adjuvant treatment	
Chemotherapy, *n* (%)	
No	1531 (62.5)
Yes	557 (22.7)
Unknown/missing	361 (14.7)
Radiotherapy, *n* (%)	
No	1953 (79.8)
Yes	98 (4.0)
Unknown/missing	398 (16.3)

CI, confidence interval; BMI, body mass index; R, right; L, left.

8.1% of the cohort consists of large cell, adenosquamous, combined/mixed, and sarcomatoid subtypes. The stage distribution is as follows: IA 22.9%, IB 26.3%, IIA 16.9%, IIB 11.9%, IIIA 20.4%, and IIIB 1.6%. The majority of tumors are reported as right upper lobe (30.9%), followed by left upper lobe (27.2%), left lower lobe (15.6%), and right lower lobe (13.9%). The median tumor size was 3.5 cm (range, 0.2–16.0 cm). Most patients have undergone radical resection, including lobectomy in 73.1%, pneumonectomy in 13.6%, and bilobectomy in 6.4%. The majority of patients underwent open thoracotomy (91.7%), whereas thoracoscopy was reported in only 4.8% of patients. Adjuvant chemotherapy was administered to 22.7% of patients, including 10.6%, 29.8%, and 40.7% of patients with stages I, II, and III, respectively. Only 4.0% received postoperative radiotherapy, including 3.3% and 12.3% of patients with stages II and III, respectively.

Comparing the baseline characteristics between patients with adenocarcinoma and squamous cell carcinoma, previous history of cancer, body mass index, and adjuvant treatment (chemotherapy/radiotherapy) do not differ significantly between the histology groups (Supplementary Table 3, Supplemental Digital Content, http://links.lww.com/JTO/A687). Patients with adenocarcinoma histology are more often women (45.3% versus 20.7% for squamous), younger (median age 65.1 versus 67.1 years), never smokers (19.4% versus 6.8%), with PS of 0 (34.3% versus 28.2%), tumors of stage I (54.5% versus 44.7%), localization on the upper right lobe (35.4% versus 25.1%), and smaller tumor size (median 3.0 versus 4.0 cm). Regarding the type of surgery, patients with adenocarcinoma have more often lobectomy (79.6% versus 65.5%) and less often pneumonectomy (6.9% versus 22.0%) compared with patients with squamous cell carcinoma.

Outcome Overall and According to Pathological TNM Stage

The median time to follow-up of the whole cohort of patients is almost 5 years (59.4 months; interquartile range, 47.5–76.5 months). At the last follow-up evaluation, almost half of the patients remain without evidence of disease (1151 patients, 47.0%), whereas 143 patients (5.8%) are alive with disease. There are 1147 reported deaths, with 812 patients (33.2% of the total cohort) who died with evidence of recurrent disease and 306 patients (12.5%) who died without such evidence. The disease status is unknown in only 1.5% of patients (eight alive and 29 dead). The estimated median OS is 68.3 months, whereas OS at 5 years is 53.2%. The 5-year survival is 69.6% and 63.6% for stages IA and IB, 51.6% and 47.7% for stages IIA and IIB, and 29.0% and 13.0% for stages IIIA and IIIB, respectively ($p < 0.001$; Figure 1*A*). The observed RFS events are 1290 (52.7% of 2449 patients), whereas the median and the 5-year RFS are 52.8 months and 47.3%, respectively. The 5-year RFS is 62.5% and 57.8% for stages IA and IB, 47.9% and 43.8% for stages IIA and IIB, and 21.0% and 13.2% for stages IIIA and IIIB, respectively ($p < 0.001$; Figure 1*B*).

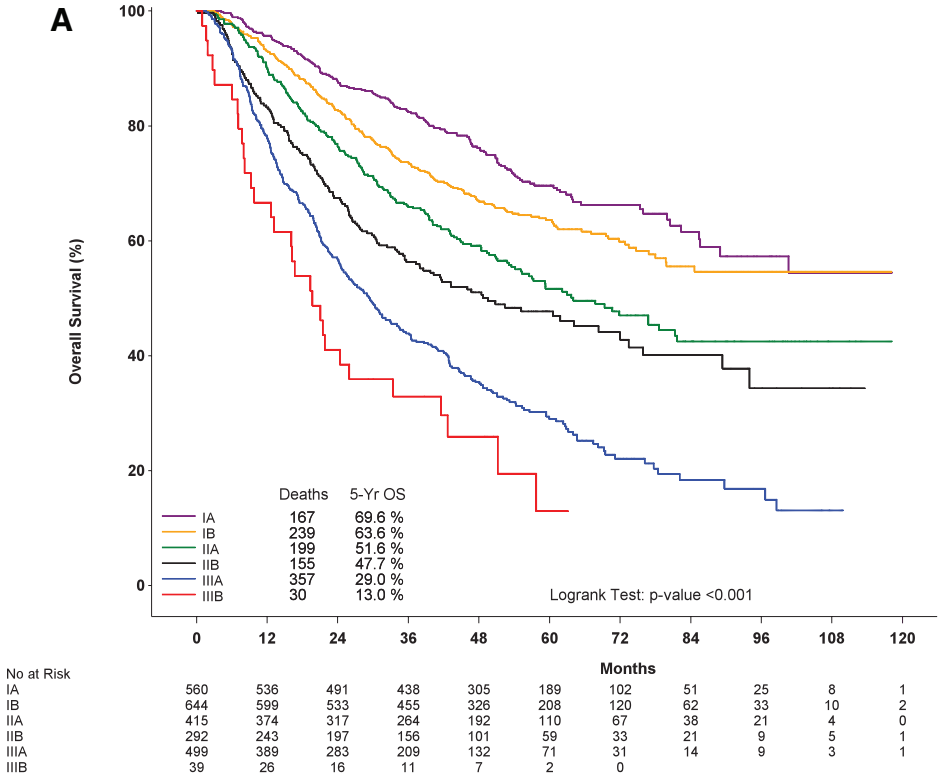
A total of 955 patients experienced a TTR event (39.0%). The median TTR is 108 months, whereas the free of relapse estimate at 5 years is 58.1%. The respective estimates by stage level are 73.6% and 69.8% for stages IA and IB, 58.0% and 53.4% for stages IIA and IIB, and 29.9% and 28.8% for stages IIIA and IIIB, respectively ($p < 0.001$; Figure 1*C*). Landmark analyses at 6, 12, 18, and 24 months indicated consistently that both RFS and TTR were strongly associated with OS (log-rank $p < 0.001$ in all).

Of the 955 patients with a relapse, 833 (87.2%) have available information on the site of relapse. Distant relapse is recorded for 44.4%, local relapse for 26.0%, and both distant and local relapse for 16.9% of the 955 patients. Within 3 years of follow-up, 67.0% of the relapses occurred with 68.4% of documented distant or combined (local and distant) relapses and 58.5% of documented local relapses occurring by 3 years. Local and distant relapses are competing risks in the TTR definition. Exploration of time-to-local and time-to-distant relapse overall and by tumor stage is presented in Figure 2*A* and 2*B*. An increasing hazard by stage is observed for both local and distant relapses ($p < 0.001$ and $p < 0.001$, excluding patients with missing site of relapse).

Influence of Clinical and Tumor Characteristics

The potential influence of patient, tumor, and treatment characteristics on outcome is assessed by both univariate and multivariate analyses. The results of the univariate analysis are summarized in Supplementary Table 4 (Supplemental Digital Content, http://links.lww.com/JTO/A687). Smoking history is associated with OS ($p = 0.048$) but not RFS and TTR. Current or former smoking is adversely affecting OS compared with never smoking (HR = 1.23, $p = 0.037$ and HR = 1.25, $p = 0.02$, respectively). OS differs significantly by sex, with median OS for female patients being higher compared with male patients (77.7 versus 62.2 months; $p = 0.0039$). A significantly higher median RFS is also observed for women compared with men (62.9 versus 48.5 months; $p = 0.008$), whereas TTR does not differ by sex. No significant difference in OS, RFS, and TTR is observed between various histologies ($p = 0.14$), except for a marginally significant difference in OS between adenocarcinoma and squamous cell histology ($p = 0.049$; Supplementary Figure 1A–C, Supplemental Digital Content, http://links.lww.com/JTO/A687).

Based on the results of the multivariate analysis for all three time-to-event end points (Figure 3*A–C*), factors in the presence of other candidate prognostic variables that are significantly associated with all three outcomes are PS (OS: 1 versus 0: HR = 1.30, $p = 0.0045$; RFS: 1 versus 0: HR = 1.30, $p = 0.0026$; TTR: 1 versus 0: HR = 1.35, $p = 0.0021$), and tumor stage (OS: HRs increasing from 1.32 for IB versus IA to 3.89 for IIIA and IIIB versus IA with all p values significant; HRs similar for RFS and TTR). Other variables significantly associated with outcome, along with PS and stage, are the following patient characteristics—for OS: sex (male versus female: HR = 1.14, $p = 0.044$), age (60–70 versus <60, HR = 1.28, $p = 0.0014$; >70 versus <60, HR = 1.45, $p < 0.0001$), and previous history of cancer (yes versus no: HR = 1.22, $p = 0.021$); for RFS: age (60–70 versus <60, HR = 1.24, $p = 0.0027$; >70 versus <60, HR = 1.36, $p < 0.001$) and type of surgery—anatomy (all others versus lobectomy: HR = 1.31, $p = 0.012$); and for TTR: histology (adenocarcinoma versus squamous:



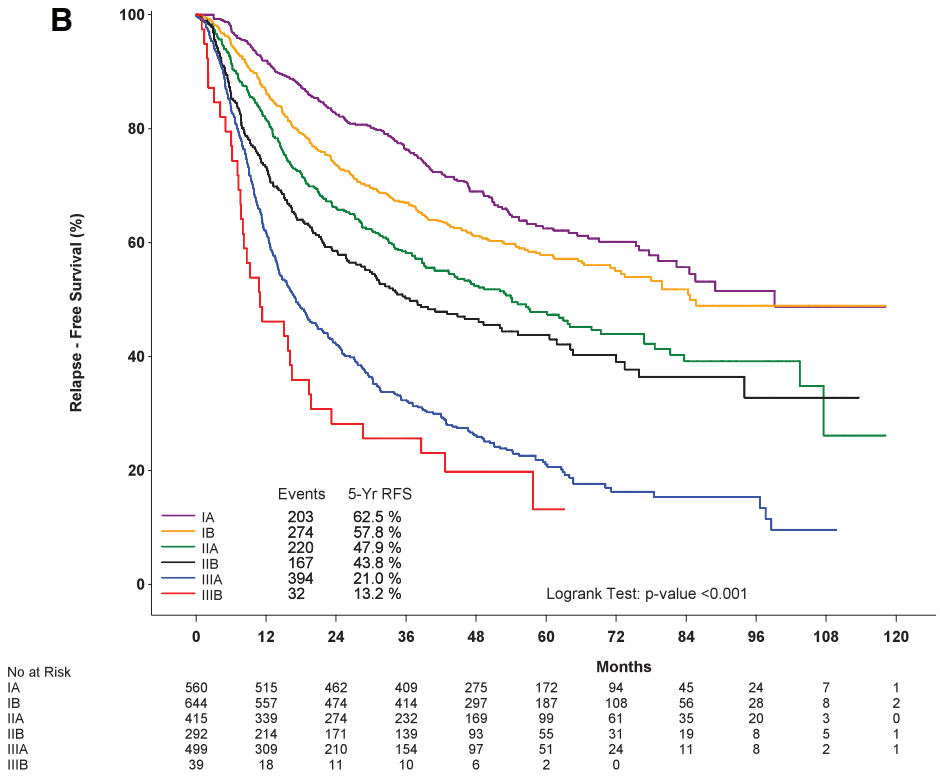


FIGURE 1. *A*, Overall survival (OS) by pathological stage. *B*, Relapse-free survival (RFS) by pathological stage. *C*, Time to relapse (TTR) by pathological stage.

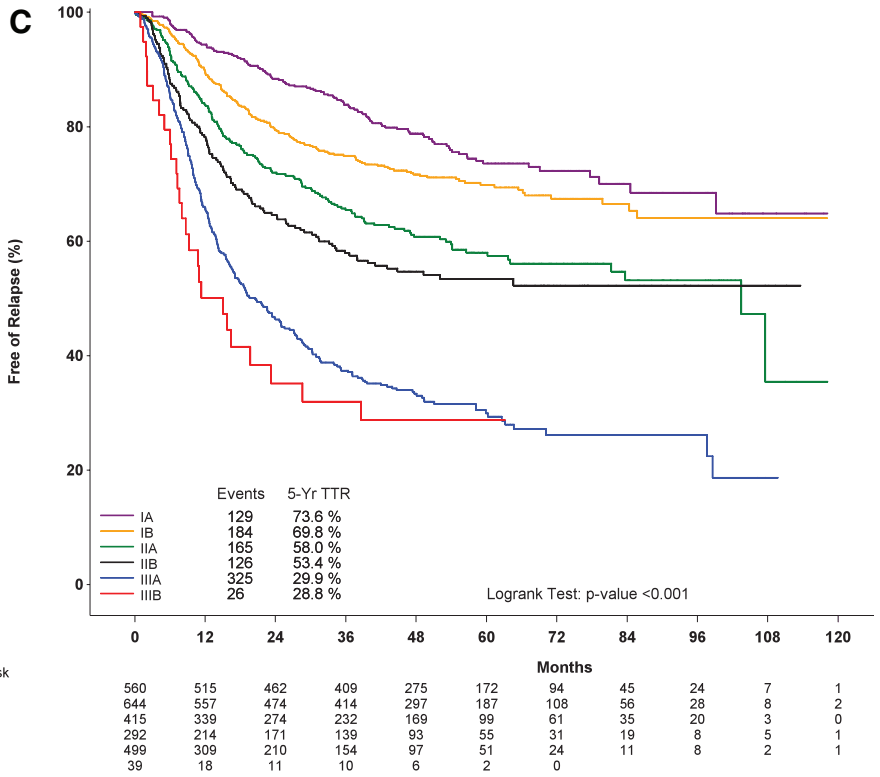


FIGURE 1. (*Continued*)

HR = 1.19, $p = 0.014$). Adjuvant chemotherapy did not have a differential effect on the survival of patients with or without the high-risk features of tumor size above 4 cm or visceral pleural involvement (Supplementary Table 5, http://links.lww.com/JTO/A687). For stage III, where 40% of patients received adjuvant chemotherapy, additional analyses showed a treatment benefit for OS (chemotherapy versus no: HR = 0.787, $p = 0.040$), a finding that was not significant for stages I and II (interaction $p = 0.020$).

No other patient, tumor, or treatment characteristic is found to be significantly associated with any of the three time-to-event outcomes in the presence of other variables. In addition, no significant interaction is detected between the variables.

DISCUSSION

The Lungscape project was launched by the European Thoracic Oncology Platform to study the molecular epidemiology on NSCLC by collecting the largest series of clinically annotated surgical NSCLC cases. At the time of this analysis, 2449 cases have been accepted in the database. This report is unique by providing outcome data beyond just stage and OS of a large cohort of surgically treated patients with NSCLC. It analyzes for the first time all three outcome parameters, OS, RFS, and TTR, determining the potential prognostic value of every clinicopathological characteristic in addition to the anatomical staging based on the seventh TNM classification. The RFS and TTR analyses are important to describe for this cohort because they better reflect tumor biology and are less dependent on age and other comorbidities than OS. This virtual annotated biobank also provides the basis for Lungscape's next steps aiming at describing the molecular landscape of resected NSCLC looking at several distinct molecular biomarkers and their individual influence on NSCLC disease history.

Stage by stage, the 5-year survival reported matches the survival of pathological stage NSCLC from the International Association for the Study of Lung Cancer database, which formed the basis for the seventh TNM edition.[2] The Lungscape data set is, therefore, a valid resource to examine the prognostic influence of clinical as well as molecular parameters on the outcome of resected NSCLC.

Surgical radical resection was the major selection criterion for inclusion into Lungscape. Regarding the surgical outcome, in the univariate analysis, older age was associated with worse survival for OS and RFS, and this held true in the multivariate analysis. Only 22.7% of patients in Lungscape received adjuvant chemotherapy. Although the potential impact of cisplatin-based adjuvant chemotherapy was first demonstrated in 1995, general acceptance in clinical practice occurred only gradually after publication of the International Adjuvant *Lung Cancer* Trial and further meta-analyses.[1,6–8] Adjuvant radiotherapy was recorded in 4.0% of patients. A beneficial effect of postoperative radiotherapy for patients with stage III (N2) NSCLC has been suggested by a retrospective analysis of the *Adjuvant Navelbine International Trialist Association* trial[9] as well as the Surveillance, Epidemiology, and End Results database.[10] In our cohort, 40% of the patients with stage III disease received adjuvant chemotherapy, which was found to benefit their OS, whereas 12.3% of the stage III patients received postoperative radiotherapy, without significant improvement in their outcome (data not shown).

Relapse was documented in 995 patients, with 58.5% documented local relapses and 68.4% distant or combined

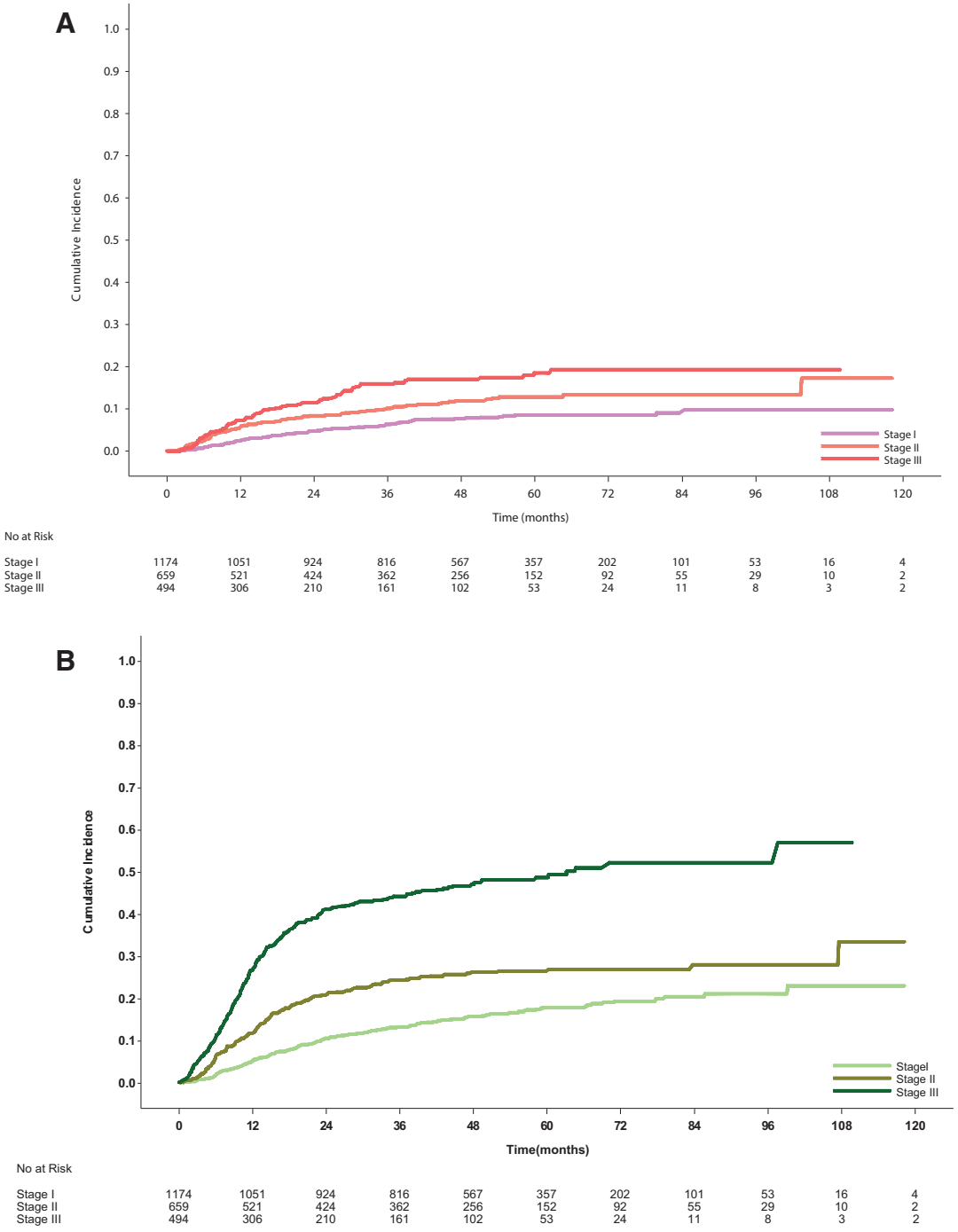
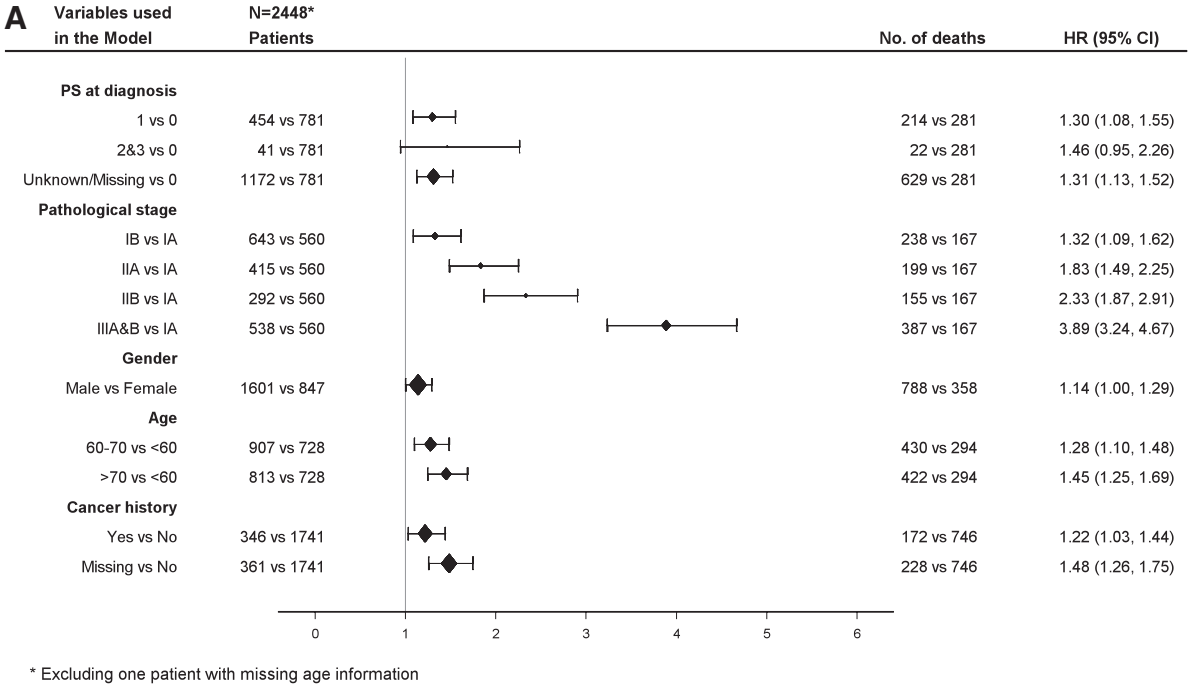


FIGURE 2 , *A*, CUMULATIVE INCIDENCE PLOT FOR TIME-TO-LOCAL RELAPSE ACCORDING TO PATHOLOGICAL STAGE. *Note*: Pathological stage categories combined as "I," "II," and "III." *B*, Cumulative incidence plot for time-to-distant and combined relapse according to pathological stage. *Note*: Pathological stage categories combined as "I," "II," and "III."

local and distant relapses occurring within the first 3 years after surgery. Pathological stage was associated with an increased risk of local as well as distant relapses. These patterns of relapse could inform future guidelines on follow-up schedules and support published expert opinion–based recommendations on the close follow-up of surgically treated patients for up to 3 years.[11] Due to the retrospective nature of this study, there was no uniform mode of follow-up. This might have minimal impact on RFS and TTR estimation. However, in the major academic center setting of this study, patients were seen at least every 6 months after surgery for the subsequent 3 years, including a radiological assessment. These data thus reflect the real life situation where evidence as to the optimal follow-up of patients after curative surgery is

still lacking. It is important to note that, in repeated landmark analyses, the association of OS with RFS as well as with TTR was consistently found significant, a finding worth further exploration with additional methodology. As of to date, there are no evidence-based recommendations for optimal follow-up after surgery. At a time when advances in radiotherapy techniques offer additional treatment options with curative intent, follow-up might become especially important in the detection of local relapse. By multivariate analysis, histology was found to be significantly associated with TTR with a worse outcome for adenocarcinoma compared with squamous cell carcinoma. A similar differential effect was seen in the control group of the *Adjuvant Navelbine International Trialist Association* trial with respect to survival[12] and in several surgical series



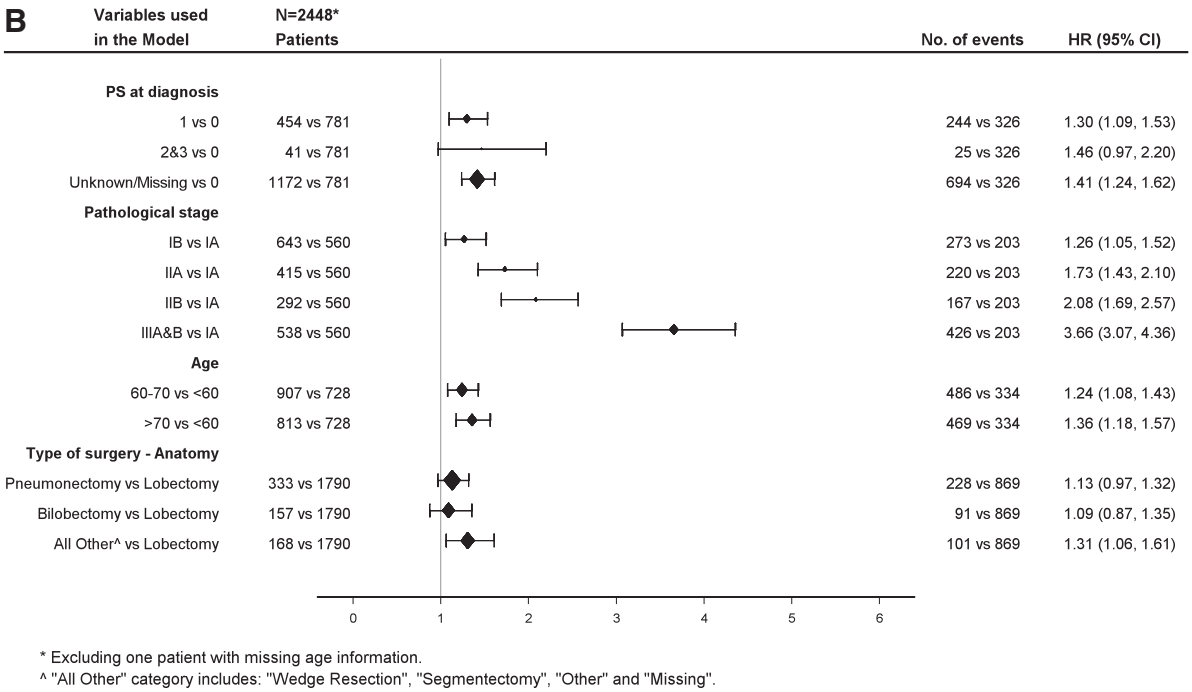


FIGURE 3. *A,* Forest plot for the multivariate overall survival Cox model. *B,* Forest plot for the multivariate relapse-free survival Cox model. *C,* Forest plot for the multivariate time-to-relapse Cox model. HR, hazard ratio; CI, confidence interval; PS, performance status.

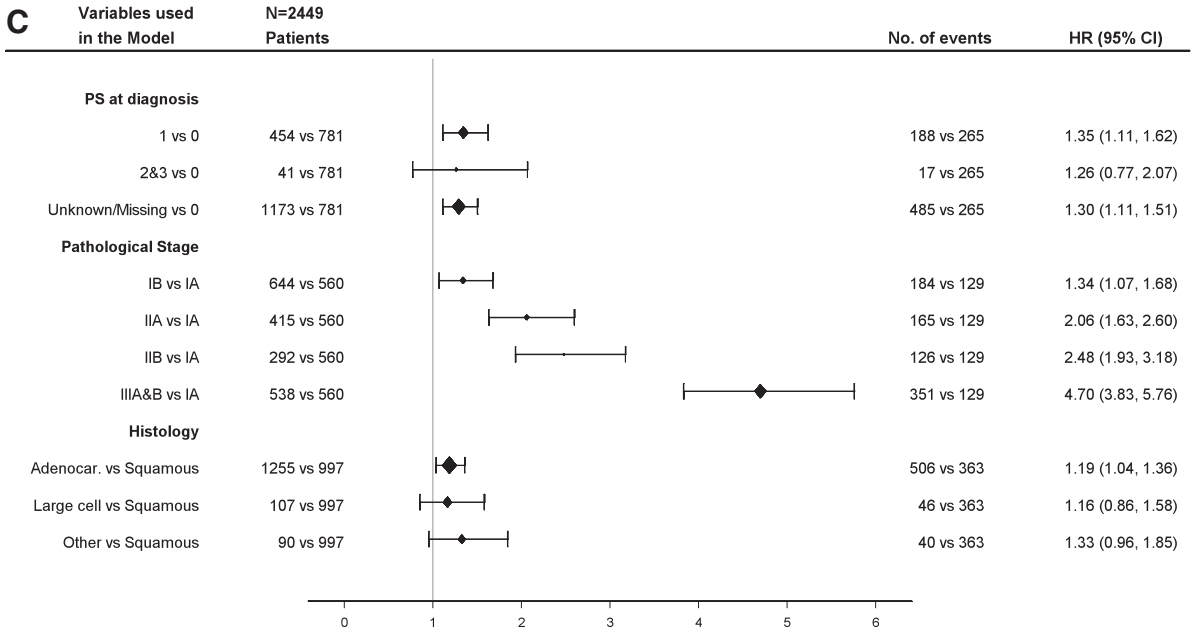


FIGURE 3. (*Continued*)

demonstrating a worse survival[13] and a higher likelihood of any relapse[14] and/or distant relapse[15] in adenocarcinoma histology. Lung Cancer Study Group trials in 1121 surgically treated patients showed superior postoperative outcome for patients with squamous cell carcinoma over nonsquamous histology in all pTN categories and for survival in all but stage III disease.[16] Higher PS was significantly associated with a poorer outcome. Our data confirm the report on prognostic factors in addition to stage in the *International Association for the Study of Lung Cancer* database, where PS was identified as a very important additional factor.[13] Smoking history was obtained for 95.5% of patients in our database. A significant difference when comparing never with current and former smokers was only detected by univariate analysis for OS. Although there is evidence that smoking had a negative influence on outcome of patients with advanced-stage disease,[17] data on smoking impact in large surgical series are scarce. Wu et al [18] reported that never smokers had a significantly better cancer-specific survival rate of 5 years after surgery than smokers, although histological subtype and stage were not taken into account. A recent series from Liverpool identified smoking as a risk for resected adenocarcinoma but not for squamous cell carcinoma,[19] and similar findings have been reported from Korea.[20] Our multivariate analysis findings on OS are in line with most of the previous reports demonstrating that male patients have a worse outcome after surgery.[21–24] A large population-based Taiwan cancer registry demonstrated that women with lung cancer had a better median and 5-year survival.[25]

Lungscape is the first large series reporting on lung cancer surgical outcome measured not only by OS but also by RFS and TTR and presenting multivariate analysis including most of the significant clinical and pathological prognostic parameters reported to date. As tissue from all patients has been preserved locally and is available for detailed molecular investigations, Lungscape provides an excellent basis to evaluate the influence of molecular parameters on the disease outcome after radical resection, in addition to providing an overview of the molecular landscape of stage I to III NSCLC. The first such project on ALK translocations has been completed and communicated.[26] Ongoing projects include MET, P13K, and PTEN, and multiplex mutation testing.

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